

Epithelial ovarian carcinoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

S. Aebi¹ & M. Castiglione²

On behalf of the ESMO Guidelines Working Group*

¹Breast/Gynecologic Cancer Center and Department of Medical Oncology, Inselspital, Bern, Switzerland; ²Bern, Switzerland

incidence

The crude incidence of ovarian cancer in the European Union is 18, the mortality is 12/100 000 women/year. The median age at diagnosis is 63 years. The incidence increases with age and peaks in the eighth decade. Between the ages of 70 and 74 years the age-specific incidence is 57/100 000 women/year.

diagnosis

The definitive diagnosis of epithelial ovarian cancer requires a surgical specimen. Pathological diagnosis should be made according to the World Health Organization classification. Established subtypes are: serous, mucinous, endometrioid, clear cell, Brenner, mixed and undifferentiated carcinomas.

staging and risk assessment

Surgical staging requires a median laparotomy with a thorough examination of the abdominal cavity according to Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) classification guidelines. If disease appears confined to the ovary, biopsy of the diaphragmatic peritoneum, paracolic gutters, pelvic peritoneum and an infracolic omentectomy, and sampling or dissection of para-aortic and pelvic nodes are required in addition to peritoneal washings.

Surgery should be performed by an appropriately trained gynaecologic oncologist with experience in the management of ovarian cancer [III, B].

Staging is described using the FIGO and American Joint Committee on Cancer (AJCC) classification and FIGO as in the table below.

Established favorable prognostic factors besides surgical stage are: small tumor volume (before and after surgery), younger age, good performance status, cell type other than mucinous or

clear cell, well-differentiated tumor and absence of ascites. Low grade, absence of dense adhesions, minimal ascites, subgroups a/b versus c and cell type other than clear cell are considered good prognostic factors for patients with stage I disease.

Before surgery and/or chemotherapy, patients should have an abdomino-pelvic CT scan, chest X-ray, serum CA125, complete blood count and differential, and biochemistry for renal and hepatic function.

treatment plan

The selection of the type of surgery and postoperative chemotherapy depends upon the stage and other clinicopathological prognostic factors.

early stage disease, FIGO I and IIa

Surgery should involve total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, random peritoneal biopsies including the paracolic gutters and at least pelvic/para-aortic lymph node sampling performed as described above. In younger patients wanting to conserve fertility with localized, unilateral tumors (stage I) and favorable histology, unilateral salpingo-oophorectomy may not be associated with a high risk of recurrence. Wedge biopsy of the contralateral ovary should be performed, if the contralateral ovary is not normal on inspection. FIGO stage I tumors with dense adhesions to other pelvic structures should be 'upstaged' and treated as FIGO II tumors, as the relapse rate appears to be similar.

FIGO stage Ia/b, welldifferentiated, non-clear cell histology: surgery alone is adequate [I, A]. FIGO stage Ia/b poorly differentiated, densely adherent, clear cell histology and all grades FIGO stage Ic and IIa: optimal surgery and staging should be performed, and adjuvant chemotherapy considered [I, A].

Consider three cycles of carboplatin [area under the curve (AUC) 5–7 mg/ml/min] + paclitaxel 175 mg/m²/3 h for early stage ovarian cancer if combination therapy is to be used [II, A]. Otherwise, six cycles of carboplatin ± paclitaxel would seem appropriate.

*Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland.

Approved by the ESMO Guidelines Working Group: April 2002, last update November 2007. This publication supercedes the previously published version—Ann Oncol 2007; 18 (Suppl 2): ii12–ii14.

Conflict of interest: Dr Aebi has reported no conflicts of interest.

advanced disease; FIGO stage IIb–IIc

Surgery should include total abdominal hysterectomy and bilateral salpingo-oophorectomy with omentectomy, with staging biopsies performed as described. Upfront maximal surgical effort at cytoreduction with the goal of no residual disease should be undertaken.

The recommended standard chemotherapy for advanced ovarian carcinoma, stages IIb–IIc is carboplatin AUC 5–7 mg/ml/min \pm paclitaxel 175 mg/m²/3 h every 3 weeks for six cycles.

If initial maximal cytoreduction was not performed, interval debulking surgery should be considered in patients responding to chemotherapy, or showing stable disease [II, B]. Interval debulking surgery should ideally be performed after three cycles of chemotherapy, followed by three further cycles of chemotherapy.

There is no evidence for a survival benefit of ‘second-look’ surgery following completion of chemotherapy in patients whose disease appears to be in complete remission. Such procedures should only be undertaken as part of a clinical trial. Likewise, the value of secondary tumor reduction at the time of second-look laparotomy is not clear.

Intraperitoneal chemotherapy should be considered an option for selected patients in centers where the expertise exists.

Neoadjuvant chemotherapy for patients considered initially not optimally resectable for either tumor or patient-related factors is a viable alternative strategy; however, available data suggest that the survival outcome may be inferior to successful primary surgery followed by chemotherapy.

advanced disease; FIGO stage IV

Patients with stage IV disease may obtain a survival advantage from being maximally surgically cytoreduced at initial laparotomy [III, B], although randomized trials have not addressed this question.

Young patients with good performance status, pleural effusion as the only site of disease outside the abdominal cavity, small volume metastases and no major organ dysfunction should be considered for surgery as outlined above.

If surgery is not planned, the diagnosis should be confirmed by biopsy and chemotherapy administered as recommended above for FIGO stage IIb–IIc disease.

response evaluation

CA125 levels during chemotherapy can accurately correlate with tumor response and with survival [III, A]. Serum CA125 should be measured at regular intervals during chemotherapy (e.g. before each cycle).

For patients with abnormal CT scan at baseline, this should be repeated after cycle 6 unless there is evidence (e.g. CA125 levels not falling) of non-responding disease; in this case an earlier CT scan would be indicated. Patients with normal CT scans at baseline do not need further CT scans, provided there is no clinical or biochemical indication of disease progression. An interim CT scan after three cycles of chemotherapy should be considered for a patient who is negative for serum CA125, or for whom interval debulking surgery is being considered.

Current data do not support a recommendation of maintenance/consolidation treatment beyond six cycles; however, the data for 12 months of paclitaxel maintenance should be discussed with patients with respect to the potential improvement observed in PFS [II, C], especially in patients with low concentrations of CA125 [III, B]. Patients with a partial response (or elevated CA125) after six cycles of chemotherapy but continuing evidence of response by CA125 can be considered for a further three cycles of the same chemotherapy [V, B].

follow-up

History, physical examination including pelvic examination every 3 months for 2 years, every 4 months during the third year and every 6 months during years 4 and 5 or until progression is documented.

CA125 can accurately predict tumor relapse [I, A], and should be performed at each follow-up visit. CT scans should be performed if there is clinical or CA125 evidence for progressive disease.

recurrent disease

Patients with long intervals (>1 year) from primary surgery should be considered for surgical resection of recurrent disease [III, A]. Patients with long intervals (>6 months) from initial chemotherapy should be offered platinum-based combination chemotherapy (carboplatin + paclitaxel, carboplatin + gemcitabine) [I, A]. For patients with short treatment-free intervals and with second and later recurrences, palliative chemotherapy with pegylated liposomal doxorubicin, gemcitabine or topotecan should be considered [II, B].

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were

Stage I	Limited to ovaries
Ia	One ovary
Ib	Both ovaries
Ic	Ruptured capsule, surface tumor or positive washings ^a
Stage II	Pelvic extension
IIa	Uterus, tube(s)
IIb	Other pelvic tissue
IIc	Positive washings, ascites
Stage III	Abdominal extension and/or regional lymph nodes
IIIa	Microscopic peritoneal metastases
IIIb	Macroscopic peritoneal metastases \leq 2cm
IIIc	Macroscopic peritoneal metastases >2 cm and/or regional lymph nodes
Stage IV	Distant metastases outside peritoneal cavity

^aFor the estimation of the prognosis, this includes iatrogenic intraoperative rupture.

considered justified standard clinical practice by the expert authors and the ESMO faculty.

literature

- Armstrong DK, Bundy B, Wenzel L et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med* 2006; 354: 34–43.
- Bell J, Brady MF, Young RC et al. Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* 2006; 102: 432–439.
- Bristow RE, Chi DS. Platinum-based neoadjuvant chemotherapy and interval surgical cytoreduction for advanced ovarian cancer: a meta-analysis. *Gynecol Oncol* 2006; 103: 1070–1076.
- Bristow RE, Eisenhauer EL, Santillan A, Chi DS. Delaying the primary surgical effort for advanced ovarian cancer: a systematic review of neoadjuvant chemotherapy and interval cytoreduction. *Gynecol Oncol* 2007; 104: 480–490.
- Bristow RE, Tomacruz RS, Armstrong DK et al. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol* 2002; 20: 1248–1259.
- du Bois A, Luck H-J, Meier W et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J Natl Cancer Inst* 2003; 95: 1320–1329.
- Fader AN, Rose PG. Role of surgery in ovarian carcinoma. *J Clin Oncol* 2007; 25: 2873–2883.
- Gordon AN, Tonda M, Sun S, Rackoff W. Long-term survival advantage for women treated with pegylated liposomal doxorubicin compared with topotecan in a phase 3 randomized study of recurrent and refractory epithelial ovarian cancer. *Gynecol Oncol* 2004; 95: 1–8.
- ICON Collaborators. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. *Lancet* 2002; 360: 505–515.
- Markman M, Liu PY, Rothenberg ML et al. Pretreatment CA-125 and risk of relapse in advanced ovarian cancer. *J Clin Oncol* 2006; 24: 1454–1458.
- Markman M, Liu PY, Wilczynski S et al. Phase III randomized trial of 12 versus 3 months of maintenance paclitaxel in patients with advanced ovarian cancer after complete response to platinum and paclitaxel-based chemotherapy: a Southwest Oncology Group and Gynecologic Oncology Group trial. *J Clin Oncol* 2003; 21: 2460–2465.
- McGuire WP, Hoskins WJ, Brady ME et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 1996; 334: 1–6.
- Ozols RF, Bundy BN, Greer BE et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: A Gynecologic Oncology Group study. *J Clin Oncol* 2003; 21: 3194–3200.
- Pfisterer J, Plante M, Vergote I et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol* 2006; 24: 4699–4707.
- Piccart MJ, Bertelsen K, James K et al. Randomized intergroup trial of cisplatin–paclitaxel versus cisplatin–cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. *J Natl Cancer Inst* 2000; 92: 699–708.
- Rose PG, Nerenstone S, Brady MF et al. Secondary surgical cytoreduction for advanced ovarian carcinoma. *N Engl J Med* 2004; 351: 2489–2497.
- Rustin GJ, Bast RC Jr, Kelloff GJ et al. Use of CA-125 in clinical trial evaluation of new therapeutic drugs for ovarian cancer. *Clin Cancer Res* 2004; 10: 3919–3926.
- Rustin GJS, Nelstrop AE PM et al. Defining response of ovarian carcinoma to initial chemotherapy according to serum CA 125. *J Clin Oncol* 1996; 14: 1545–1551.
- Trimbos JB, Parmar M, Vergote I et al. International collaborative ovarian neoplasm trial 1 and adjuvant chemotherapy in ovarian neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. *J Natl Cancer Inst* 2003; 95: 105–112.
- van der Burg ME, van Lent M, Buyse M et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med* 1995; 332: 629–634.
- Vergote I, De Brabanter J, Fyles A et al. Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma. *Lancet* 2001; 357: 176–182.